



# Role of systematic lymphadenectomy at the time of interval debulking surgery for patients with advanced-stage epithelial ovarian carcinoma who achieved complete gross resection

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## HIGHLIGHTS

- ⇒ For patients undergoing primary cytoreductive surgery evidence from randomized trials does not support the performance of systematic lymphadenectomy.
- ⇒ For patients undergoing interval cytoreductive surgery, the role of systematic lymphadenectomy is not defined.
- ⇒ Systematic lymphadenectomy was not associated with a survival benefit in a large cohort of patients undergoing interval cytoreductive surgery.

## ABSTRACT

**Objective** To evaluate the role of systematic lymphadenectomy at the time of interval cytoreductive surgery for patients with advanced-stage epithelial ovarian carcinoma who achieved complete gross resection.

**Methods** The National Cancer DataBase was accessed, and patients diagnosed between 2010 and 2015 with advanced-stage ovarian carcinoma who underwent interval cytoreductive surgery and achieved complete gross resection were identified. Patients who did not undergo lymphadenectomy and those who underwent systematic lymphadenectomy (defined as at least 20 lymph nodes removed) were selected for further analysis. Median overall survival was compared with the log-rank test and controlled for a priori selected confounders.

**Results** A total of 1060 patients were identified. Systematic lymphadenectomy was performed for 125 (11.8%) patients with a median of 29 lymph nodes (range 20–72) removed. Rate of lymph node metastasis was 62.4%. Patients who underwent systematic lymphadenectomy had higher rate of unplanned readmission (8.9% vs 1.6%,  $p<0.001$ ), and median hospital stay (6 vs 4 days,  $p<0.001$ ). Median overall survival for patients who did and did not undergo systematic lymphadenectomy was 44.2 and 40.4 months, respectively,  $p=0.40$ . After controlling for confounders, performance of systematic lymphadenectomy was not associated with better survival (HR=0.98, 95% CI 0.80 to 1.19).

**Conclusion** Systematic lymphadenectomy is rarely performed at the time of interval cytoreductive surgery and not associated with a survival benefit for patients who achieved complete gross resection.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ For patients undergoing primary cytoreductive surgery, performance of systematic lymphadenectomy is not associated with survival benefit; data for patients undergoing interval cytoreductive surgery are lacking.

## WHAT THIS STUDY ADDS

- ⇒ For patients undergoing interval cytoreductive surgery and achieving complete gross resection, performance of systematic lymphadenectomy is associated with higher peri-operative morbidity and does not confer an overall survival benefit.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ In the absence of prospective data, routine systematic lymphadenectomy at the time of interval cytoreductive surgery should be avoided.

## INTRODUCTION

Approximately 19 000 women will be diagnosed with ovarian cancer in the United States each year.<sup>1</sup> Most patients will present with advanced-stage disease and use of neoadjuvant chemotherapy in this patient population has been increasing following the publication of four randomized trials.<sup>2–5</sup> The prognostic significance of complete gross resection at the time of interval cytoreductive surgery has been demonstrated across multiple studies.<sup>6,7</sup> In the era of second-look surgery, a relatively high prevalence of residual microscopic lymph node metastasis following chemotherapy administration was observed.<sup>8</sup> Performance

## Original research

of systematic lymphadenectomy aims to remove lymph nodes that can serve as sanctuary sites and lead to the emergence of chemotherapy-resistant tumor clones. However, for patients with advanced-stage ovarian cancer who underwent primary cytoreductive surgery and achieved complete gross resection, a recent landmark randomized trial failed to demonstrate an oncologic benefit of systematic lymphadenectomy.<sup>9</sup> To date only a small number of heterogeneous retrospective studies have examined the role of systematic lymphadenectomy in patients undergoing interval cytoreductive surgery.<sup>10–20</sup> The main limitations of these studies are the inclusion of patients with gross residual disease and small sample size. As such, the aim of the present study was to investigate the impact of systematic lymphadenectomy on the overall survival of patients with advanced-stage epithelial ovarian carcinoma who underwent interval cytoreductive surgery and achieved complete gross resection using a large multicenter hospital-based database.

## METHODS

The National Cancer DataBase was accessed, and patients diagnosed between 2010 and 2015 with a pathologically confirmed primary ovarian carcinoma and no history of another tumor were identified. Those with International Federation of Gynecology and Obstetrics (FIGO) stage III–V disease who received neoadjuvant chemotherapy (defined as chemotherapy received within 4 months prior to surgery) and achieved complete gross resection (defined as absence of visible disease) following interval cytoreductive surgery were selected for further analysis. Performance of systematic lymph node dissection and number of lymph nodes removed was evaluated from the pathology report. Two groups were formed for analysis purposes: no lymphadenectomy and systematic lymphadenectomy (defined as at least 20 lymph nodes removed). We opted to select a 20-lymph node cut-off point to exclude patients who had resection of grossly abnormal lymph nodes alone and underwent lymph node debulking alone similar to prior analysis.<sup>21</sup> Patient selection flowchart is depicted in Online supplemental figure 1.

Primary outcome was median overall survival while secondary outcomes included peri-operative morbidity; 90-day mortality rate, 30-day unplanned readmission rate, median inpatient hospital stay, and rate of prolonged hospital stay (defined as >10 days). In addition, for patients undergoing lymphadenectomy overall survival based on lymph node status was evaluated. Demographic and clinicopathological data were extracted from the de-identified dataset. Categorical and continuous variables were compared with the  $\chi^2$  or Fisher's exact test and Mann-Whitney U tests, respectively. Kaplan-Meier curves were generated to determine median overall survival and compared with the log-rank test. A Cox multivariate model was constructed to control for a priori selected confounders known to be associated with overall survival.

The National Cancer DataBase was established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons, as a hospital-based database capturing data of approximately 70% of patients with newly diagnosed cancer in the United States. Patient data are prospectively collected from participating commission-accredited cancer programs and are regularly audited. All data are de-identified and available for research

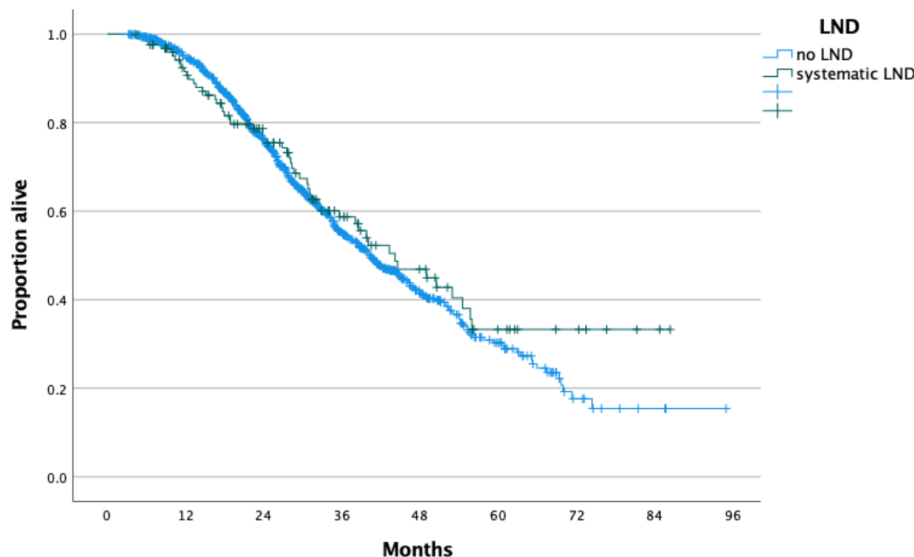
**Table 1** Clinicopathological characteristics of patients undergoing interval cytoreductive surgery and achieving complete gross resection, stratified by performance of systematic lymphadenectomy (LND)

	No LND (n=935)	LND (n=125)	
Age (years)			0.007
≤65	501 (53.6%)	83 (66.4%)	
>65	434 (46.4%)	42 (33.6%)	
Race			0.85
White	821 (87.8%)	109 (87.2%)	
Other/unknown	114 (12.2%)	16 (12.8%)	
Co-morbidities			0.63
No	738 (78.9%)	101 (80.8%)	
Yes	197 (21.1%)	24 (19.2%)	
Insurance			0.004
Private	391 (41.8%)	71 (56.8%)	
Government	499 (53.4%)	52 (41.6%)	
Uninsured/unknown	45 (4.8%)	(n<10)	
Reporting facility			0.42
Academic	411 (44.5%)	50 (40.7%)	
Non-academic	512 (55.5%)	73 (59.3%)	
Histology			0.015
Serous	901 (96.4%)	114 (91.2%)	
Non-serous	34 (3.6%)	11 (8.8%)	
Grade			0.96
Grade 1–2	52 (5.6%)	(n<10)	
Grade 3	655 (70%)	86 (68.8%)	
Unknown	228 (24.4%)	32 (25.6%)	
Stage			0.69
Stage III	608 (65%)	79 (63.2%)	
Stage IV	327 (35%)	46 (36.8%)	

purposes. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data. The present study was deemed exempt from the Penn institutional review board (protocol #829268). All statistical analyses were performed with the Statistical Package for the Social Sciences, version 29 (International Business Machines Corporation, Armonk, New York, USA), and the  $\alpha$  level of statistical significance was set at 0.05.

## RESULTS

A total of 1060 patients who met the inclusion criteria were identified. Systematic lymphadenectomy was performed for 125 (11.8%) patients, with a median of 29 lymph nodes (range 20–72) removed. Rate of lymph node metastasis confirmed by pathologic evaluation was 62.4%, while the median number of positive lymph nodes was 5 (range 1–28). **Table 1** depicts the clinicopathological characteristics of patients who did and did not undergo systematic



ms	0	12	24	36	48	60	72	84	96
No LND	935	814	535	276	116	47	10	3	0
LND	125	104	71	41	25	11	6	1	0

**Figure 1** Comparison of overall survival of patients with stage III-IV ovarian cancer with complete gross resection at time of interval cytoreductive surgery who did and did not undergo systematic lymphadenectomy (LND).

lymphadenectomy. Patients who underwent systematic lymphadenectomy were younger (median 61 vs 64 years,  $p=0.007$ ), and more likely to have non-serous histology (8.8% vs 3.6%,  $p=0.015$ ). However, disease stage and tumor grade distribution were comparable between the two groups. Demographic characteristics such as patient's race, and presence of co-morbidities were also comparable between the two groups. There was no difference in the rate of systematic lymphadenectomy between academic and non-academic institutions (12.5% vs 10.8%,  $p=0.42$ ). Lastly no temporal trends in the performance of systematic lymphadenectomy were observed (14.3% in 2010, 8.6% in 2011, 13% in 2012, 14% in 2013, 11.5% in 2014, and 10.4% in 2015).

Based on the reverse Kaplan-Meier method, median follow-up of the present cohort was 38.2 months. Median overall survival of patients who did not undergo systematic lymphadenectomy was 40.4 months (410 deaths) compared with 44.2 months (54 deaths) for those who did,  $p=0.40$ . (Figure 1). After controlling for patient age, insurance status, race, presence of co-morbidities, histology, and disease stage, performance of systematic lymphadenectomy was not associated with better survival (HR=0.98, 95% CI 0.80 to 1.19). Among patients who underwent systematic lymphadenectomy and had positive lymph nodes ( $n=78$ ), the 4-year overall survival rate was 39.7% compared with 55.8% for those with negative lymph nodes ( $n=47$ ) ( $p=0.12$ ) (Figure 2).

Regarding peri-operative morbidity, patients who underwent systematic lymphadenectomy had a higher rate of unplanned readmission within 30 days from discharge (8.9% vs 1.6%,  $p<0.001$ ), as well as longer hospital stay (median 6 vs 4 days,  $p<0.001$ ). However, rate of prolonged hospital stay (defined as >10 days) (6.1% vs 4.2%,  $p=0.33$ ) and 90-day mortality were comparable between the two groups (0.9% vs 1.7%,  $p=0.33$ ).

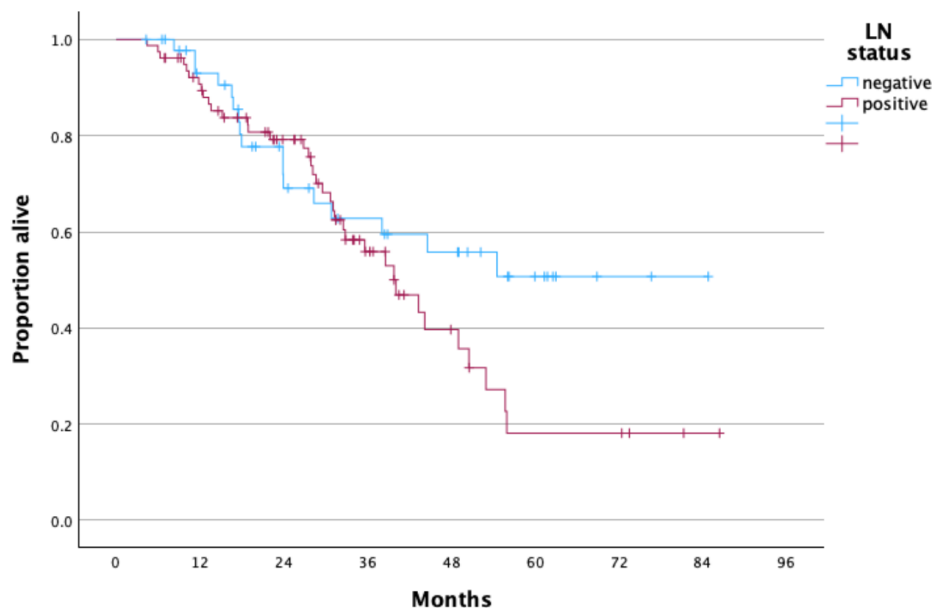
## DISCUSSION

### Summary of Main Results

Based on real-world data, for patients with advanced-stage ovarian carcinoma who underwent interval cytoreductive surgery and achieved complete gross resection, systematic lymphadenectomy was rarely performed. While a high prevalence of pathologically confirmed lymph node metastasis was observed, performance of systematic lymphadenectomy was not associated with an overall survival benefit even after controlling for confounders. On the other hand, systematic lymphadenectomy was associated with significant increase in peri-operative morbidity.

### Results in the Context of Published Literature

Several studies have demonstrated a high prevalence of lymph node metastasis among patients with advanced-stage epithelial ovarian carcinoma, even following the completion of chemotherapy.<sup>8,22</sup> However, the oncologic benefit of systematic lymphadenectomy at the time of interval cytoreductive surgery is not well defined. Caruso et al recently performed a systematic review of the literature and meta-analysis.<sup>20</sup> Authors identified a total of nine retrospective studies that included a total of 1660 patients, of whom 827 (49.8%) underwent systematic lymphadenectomy, 490 (29.5%) had selective lymphadenectomy and 343 (20.7%) did not have any lymphadenectomy.<sup>20</sup> It should be noted that the majority of studies (six out of nine) were performed at a single institution, while patient enrollment spanned from 1996 to 2018 and included patients with gross residual disease. Based on six studies, performance of systematic lymphadenectomy was not associated with a benefit in progression-free survival compared with limited/no lymphadenectomy (HR=0.88, 95% CI 0.65 to 1.20), although significant heterogeneity was encountered ( $I^2$  60%).<sup>20</sup> Similar to our



ms	0	12	24	36	48	60	72	84	96
Negative	47	38	24	19	15	7	2	1	0
Positive	78	66	47	22	10	4	4	1	0

**Figure 2** Comparison of overall survival of patients with stage III-IV ovarian cancer with complete gross resection at time of interval cytoreductive surgery who did and did not have positive lymph nodes following systematic lymphadenectomy (LND).

results, based on data from two studies<sup>12 15</sup> that included patients with no gross residual disease, again systematic lymphadenectomy was not associated with a progression-free (HR=1.17, 95% CI 0.81 to 1.48) or overall (HR=1.33, 95% CI 0.92 to 1.91). However, it should be mentioned that this subgroup analysis included only 285 patients.

To date, no prospective randomized trial has examined the impact of systematic lymphadenectomy on the oncologic outcomes of patients undergoing interval cytoreductive surgery. However, two prospective randomized trials have been conducted in the primary cytoreductive surgery setting.<sup>9 23</sup> Panici et al<sup>23</sup> randomly assigned patients with optimally debulked (residual disease  $\leq 1$  cm) stage IIIB-C/IV ovarian carcinoma to systematic pelvic and para-aortic lymphadenectomy (n=216) or removal only of bulky lymph nodes (n=211).<sup>22</sup> Patients who underwent comprehensive lymphadenectomy had better progression-free survival (HR=0.75, 95% CI 0.59 to 0.94), but there was no benefit in terms of overall survival (HR=0.97, 95% CI 0.74 to 1.29). However, it should be noted that only 37% of patients enrolled achieved complete gross resection.<sup>23</sup> More recently, the well designed LION randomized trial, prospectively enrolled 647 patients with stage IIB-IV epithelial ovarian carcinoma with no pre-operative or intra-operative macroscopically enlarged nodes, who achieved complete gross resection at the time of primary debulking surgery.<sup>9</sup> While the incidence of lymph node metastasis in the systematic lymphadenectomy group was 55.7%, there was no difference in overall survival (lymphadenectomy group median 65.5 months versus 69.2 months in no lymphadenectomy group, p=0.65) or progression-free survival, respectively (median 25.5 months in both groups, p=0.29).<sup>9</sup>

In our study patients who underwent systematic lymphadenectomy had longer hospital stay and higher rates of unplanned readmission within 30 days from surgery. Data from retrospective and prospective studies consistently report increased peri-operative morbidity when systematic lymphadenectomy is performed at the time of ovarian cancer cytoreductive surgery.<sup>9 20</sup> In the LION trial patients who underwent systematic lymphadenectomy had longer total operative time (median 340 vs 280 min, p<0.001), larger blood loss (median 650 vs 500 mL, p<0.001), higher rates of blood transfusion (63.7% vs 56%, p=0.005), higher rate of admission to intensive care unit (77.6% vs 69%, p=0.01), and increased 60-day mortality.<sup>9</sup> Similar to our results, a meta-analysis of retrospective studies reported increased peri-operative morbidity among patients undergoing systematic lymphadenectomy at the time of interval cytoreductive surgery.<sup>20</sup> Based on 1336 patients from seven studies who underwent systematic lymphadenectomy had higher odds (OR=1.83, 95% CI 1.19 to 2.82) of experiencing a grade III-IV post-operative complication.<sup>20</sup> They also had higher odds of developing lymphedema (two studies, 566 patients, OR=7.23, 95% CI 3.4 to 15.36) or lymphocele (four studies, 850 patients, OR=3.38, 95% CI 1.71 to 6.7). Four out of five studies also reported increased operative time if systematic lymphadenectomy was performed.

### Strengths and Limitations

A major strength of the present study is the inclusion of a large modern cohort of patients managed across multiple Commission on Cancer accredited institutions in the United States. In addition, contrary to prior studies our study focused only on patients who achieved complete gross resection. However, several limitations

should be mentioned. Firstly, given the absence of central pathology review possible histology and staging misclassifications cannot be excluded, while for 25% of patients tumor grade was not available suggesting possible uncertainty regarding tumor histology. In addition, the National Cancer DataBase does not collect data on tumor relapse precluding us from analyzing differences in progression-free survival and patterns of tumor recurrence. Data on the status of lymph nodes based on pre-operative imaging and intra-operative assessment were not available. As such, we could not determine how many patients included in the comprehensive lymphadenectomy group had lymph nodes suspicious for metastases based on imaging or intra-operative evaluation. Also, location of lymph nodes removed (pelvic vs para-aortic), type of metastases (micrometastases or macrometastases), and details of the surgical procedures performed, such as upper limit of dissection (eg, inferior mesenteric artery vs renal vessels), were not available. Details of the total operative time, blood loss or specific peri-operative complications, as well as data on the number of chemotherapy cycles and agents used, or details of maintenance treatment are not collected in the database. Moreover, the study spanned between 2004 and 2015, a time period when use of maintenance treatment with bevacizumab and PARPi may have not been fully implemented. Lastly, even though the two study groups were comparable for baseline demographic and pathologic characteristics, unmeasured factors that could potentially influence surgeons' decision to perform lymphadenectomy were not reported.

### Implications for Practice and Further Research

While removal of radiologic or grossly enlarged lymph nodes at the time of interval cytoreductive surgery should be performed, results of our study support the omission of systematic lymphadenectomy at the time of interval cytoreductive surgery. A randomized trial would provide definitive evidence; however, given the negative results of the LION trial, and lack of a signal of survival benefit across multiple retrospective studies, resources would be best allocated to the evaluation of novel maintenance treatment strategies or other surgical interventions (eg, heated intraperitoneal chemotherapy) in the interval cytoreductive surgery setting.

### CONCLUSIONS

In a large cohort of patients with advanced-stage ovarian cancer who received neoadjuvant chemotherapy and achieved complete gross resection at the time of interval cytoreductive surgery, performance of comprehensive lymphadenectomy was not associated with an overall survival benefit but was associated with higher peri-operative morbidity.

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